EXHIBIT K

IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: BOSTON SCIENTIFIC CORP., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION — **MDL NO. 2326**

This document relates to:

ALL WAVE 1 AND 2 CASES IN MDL NO. 2326

RULE 26 EXPERT REPORT OF SCOTT GUELCHER, Ph.D.

The following report is provided pursuant to Rule 26 of the Federal Rules of Civil Procedure. The opinions which are held and expressed are as follows:

I. QUALIFICATIONS

I received my Bachelor's Degree in Chemical Engineering from Virginia Tech in 1992, my Master's Degree in Chemical Engineering from the University of Pittsburgh in 1996, and my Ph.D. in Chemical Engineering from Carnegie Mellon University in 1999. I completed my training as a Post-Doctoral Research Associate in Biomedical Engineering at Carnegie Mellon University in 2005.

I have been an Associate Professor in the Department of Chemical and Biomolecular Engineering at Vanderbilt University since 2012, and prior to that I was an Assistant Professor in that department from 2005 through 2012. I have taught many courses at Vanderbilt, including Chemical Reaction Engineering, Polymer Science and Engineering, Bioprocessing Engineering, Introduction to Engineering, Molecular and Cell Biology for Engineers, and Product and Process Design.

My professional experience includes: Senior Associate Scientist at Bayer Corporation, Polyurethanes Division, in South Charleston, West Virginia from 2002-2003; Associate Scientist at Bayer Corporation, Polyurethanes Division from 1999-2001; Trainee at Philips Research, in Eindhoven, The Netherlands in 1998; Limited Service Employee at Eastman Chemical Co. from 1995-1997; and Chemical Engineer at Eastman Chemical Co. from 1992-1994.

I a co-editor of the book, *An Introduction to Biomaterials*, SA Guelcher and JO Hollinger, eds., Boca Raton: CRC Press 2006. I am also the author of several book chapters, including, but not limited to, SA Guelcher, Polyurethanes. In *An Introduction to Biomaterials*, 161 – 183. SA Guelcher and JO Hollinger, eds. Boca Raton, CRC Press 2006; SA Guelcher and JO Hollinger, Introduction. In *An Introduction to Biomaterials*, 1 – 2. SA Guelcher and JO Hollinger, eds. Boca Raton, CRC Press 2006; and SA Guelcher, Biocompatibility of Injectable Materials. In *Injectable Biomaterials: Science and Applications*. B Vernon, ed. Woodhead Publishing 2011; and EM Prieto and SA Guelcher, Tailoring Properties of Polymeric Biomedical Foams. *In Biomedical Foams for Tissue Engineering Applications*. P Netti, ed. Woodhead Publishing 2014. My areas of research include biomaterials design and development, drug and gene delivery, tissue engineering, and *in vitro* models for cancer metastasis.

My experience, education and training and a complete list of my published articles are summarized in my Curriculum Vitae attached to this report as Exhibit A. I have published 62 peer-reviewed articles, including two on the design of scaffolds that degrade in response to secretion of reactive oxygen species by infiltrating cells. I have given 47 invited presentations and co-authored 152 abstracts presented at scientific meetings. I have also submitted 13 abstracts to future scientific meetings, three of which relate to oxidation of polypropylene in biomedical devices. I am a co-inventor on 9 issued U.S. and European Patents and 20 pending applications.

II. SUMMARY OF OPINIONS

This report is an examination and assessment of the polypropylene mesh utilized in the Boston Scientific Stress Urinary Incontinence and Pelvic Organ Prolapse devices. All of the opinions presented herein are made to a reasonable degree of scientific certainty and within my field of expertise.

1) Polypropylene reacts with molecular oxygen by autoxidation outside the body at elevated temperatures, resulting in chain scission and deterioration of its mechanical properties;

2) After implantation, the surface of a polypropylene mesh reacts with reactive oxygen species that are secreted by inflammatory cells in the body, causing it to chemically degrade;

3) The human body does not stop responding to the polypropylene mesh used in these devices unless the mesh is removed in its entirety;

4) These devices are intended to last for the lifetime of the patient, but it is not possible to guarantee that they will perform their intended function after implantation;

5) The environment where these meshes are implanted, when coupled with the foreign body reaction, causes the properties to change and deteriorate, which can lead to adverse events in an implantee; and

6) Boston Scientific did not consider several principles of biomaterials science by not testing the stability of its meshes in an oxidative environment representative of the foreign body reaction in the human body.

III. BACKGROUND

Boston Scientific ("BSC") sells permanently implantable polypropylene-based meshes intended to treat Stress Urinary Incontinence ("SUI") and Pelvic Organ Prolapse ("POP"). The meshes examined for this report were all made from the same base resin, Marlex HGX-030-01.[1] This resin is purchased in pellet form and then heat-spun into monofilament fibers, which are then knit into different mesh constructions.[2] There are two mesh constructions that are at issue for this report: the Advantage Mesh line, which is used in the Advantage, Obtryx, Lynx and Prefxy SUI products; and Proxy Biomedical's Polyform product line, which includes the BSC Pinnacle and Uphold POP products.[3] The density is different between the Advantage and Polyform meshes (100 grams per meter squared compared to 50 grams per meter squared, respectively)[4] and so is the pattern in which they are knit, but both constructions are intended for permanent implantation in the female pelvis and both are made from the same raw material, Marlex HGX-030-01.[5]

IV. DISCUSSION

1) Polypropylene Reacts with Molecular Oxygen Outside the Body by the Process of Autoxidation

Polypropylene (PP) is a polymer that was introduced in the late 1950s. Polypropylene flakes and chips are generally manufactured from propylene gas, a component of natural gas. Polypropylene is generally formed by an addition reaction of the monomer propylene into polymers. After this polymerization occurs, the fiber is typically melt-spun as filaments, where a single fiber strand is referred to as a monofilament. The principle chemical structure of the polypropylene formed during this process is called "isotactic polypropylene" and it is shown in Figure 1.[6]

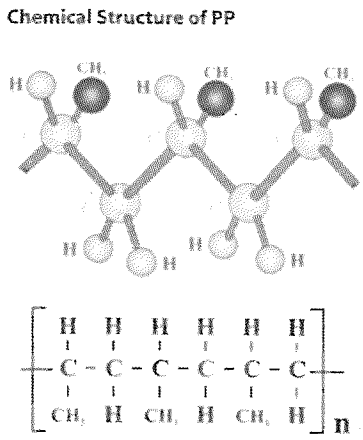

Figure 1. Chemical structure of polypropylene.

There are three general classifications of PP currently manufactured. Each of these types of PP has particular properties.

- Homopolymers comprise a general-purpose grade of PP used in a variety of different applications.
- Block copolymers incorporate 5-15% ethylene and have improved impact resistance compared to homopolymers. Their toughness can be further

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[1] BSCM05100122946
[2] Id.
[3] Id.
[4] BSCM06100029429
[5] BSCM05100122946
[6] Industrial Polymers, 2008, p. 74

enhanced by the addition of impact modifiers, which are traditionally elastomers blended into the PP.

- Random copolymers incorporate co-monomer units that are arranged randomly (as distinct from discrete blocks) along a PP molecule. Such polymers typically contain 1-7% ethylene and are selected when a lower melting point, more flexibility, and enhanced clarity are advantageous.

Different PP grades within each classification are available and can be chosen dependent on the application and processing method. It is possible to tailor grades of PP with specific molecular properties and additives during manufacturing or during the extrusion part of the melt spinning process. Some examples of additives often incorporated into PP include antioxidants, neutralizing agents, antistatic agents, slip agents, and UV stabilizers.[7] Thus, the intended use of the polymer becomes critical, since the manufacturer can incorporate additives designed to preserve the initial properties for as long as possible under the environmental conditions where it will be used.

3.5.2 Polypropylene

3.5.2.1 Physical properties of polypropylene (Table 3.10)

Table 3.10 Physical properties of polypropylene

	PP Homo	PP Copo	PP Impact
Optical	Transparent to opaque	Opaque	Opaque
T_g (°C)	−5	−20	−35
H_2O Absorption	0.01	0.01	0.01
Oxidation resistance	Low, oxides readily	Low, oxides readily	Low, oxides readily
UV resistance	With stabilization high	With stabilization high	With stabilization high

Table 1. PP oxidative resistance (REF).

All forms of PP are susceptible to oxidative degradation, as shown in Table 1.[8] PP is reported to have the highest tendency for oxidative degradation compared to other common commodity polymers, as shown in Figure 2.[9]

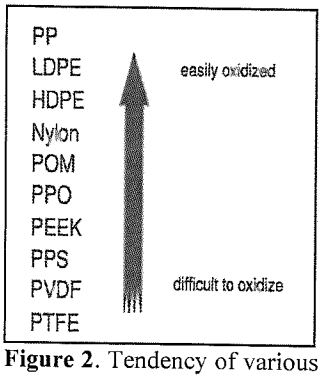

Figure 2. Tendency of various polymers to undergo oxidation (REF).

Degradation of PP occurs when the polymer is placed under stress, which can be environmental factors such as heat, light, or mechanical forces. Stresses can also be more chemical in nature, including acids, alkalis, or oxidative species. The effect of these stresses can include the loss of tensile strength or changes to the appearance of the surface, color, or shape of the PP. These changes are usually undesirable, since cracking and chemical disintegration of the material will lower the molecular weight of the polymer and change its physical and mechanical properties.

[7] Industrial Polymers, 2008, p. 74.
[8] Applied Plastics Engineering Handbook, Processing and Materials, 2011, p. 44.
[9] Compositional and Failure Analysis of Polymers, 2000, p. 399.

All forms of PP are susceptible to oxidation at the weakest point in its repeating chemical structure: the tertiary hydrogen-carbon bond.[10] Oxidative attack on the hydrogen in the tertiary carbon position is the rate-controlling step in this process[11] [12], and it will result in molecular chain of PP being broken (a process known as chain scission) with the consequent loss in molecular weight. The mechanism of PP oxidation is shown in Figure 3.[13] The process is autocatalytic, resulting in generation of more PP radicals (PP•) as the reaction progresses. Thus, the reaction continues until no more PP can be broken down. The mechanism of PP autoxidation has been investigated extensively since the 1960s and was well known at the time that the Advantage and Polyform meshes were designed. As shown in Figure 3, the products of oxidation include shorter PP chains with hydroperoxide (COOH) and carbonyl (C=O) groups covalently bound to the PP. The presence of these groups can be detected by surface techniques such as Fourier Transform Infrared Spectroscopy (FTIR) and x-ray photoelectron spectroscopy (XPS) as evidence of oxidation.[14] For non-oxidized PP, 100% of the total carbon content is bound to other carbon atoms (-CH_2-). However, if the PP is oxidized, a portion of the carbon atoms will be bound to oxygen in the form of carbonyl or hydroperoxide groups (Figure 3). The basic mechanism of oxidative degradation has been identified as follows:

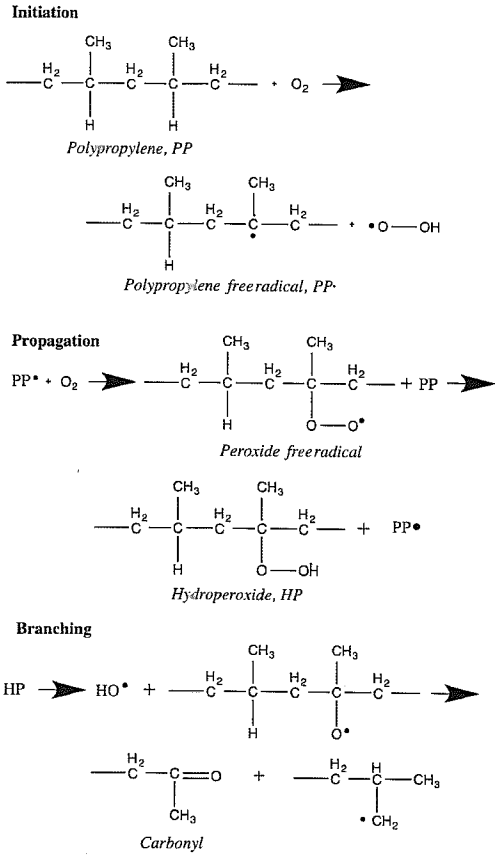

Figure 3. Mechanism of PP autoxidation. Initiation, propagation, and branching reactions lead to chain scission (loss of molecular weight). Products from autoxidation include hydroperoxide and carbonyl groups, which can be detected by analytical methods such as FTIR and XPS. Re-drawn from *The Polypropylene Handbook.*

> Oxidation in PP amorphous phase => chain scission => rupture of tie chains => loss of ductility.[15]

Furthermore, this loss of ductility through oxidative degradation leads to embrittlement of the polymer, micro-crack formation, crack propagation and ultimate PP fracture and fragmentation.

Primary and secondary antioxidants are added to PP to inhibit oxidation of the polymer,

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[10] H.H. Kausch. The effect of Degradation and Stabilization on the Mechanical Properties of Polymers Using Polypropylene Blends as the Main Example. Macromol. Symp. 2005, 225, 165-178.
[11] *Id.;* Hoff and Jacobsson. Thermal Oxidation of Polypropylene in the Temperature Range of 120-280C. J Appl Polym Sci 29:465-80,1984
[12] Polypropylene: The Definitive User's Guide and Databook, 1998, p. 6-7.
[13] Reference for Figure 1: C Maier, T Calafut. Polypropylene: The Definitive User's Guide and Databook. Norwich, NY: Plastics Design Library, 1998.
[14] Fayolle et al. Oxidation-induced embrittlement in polypropylene – a tensile testing study. Polym Degrad Stability 70:333-40, 2000
[15] Fayolle et al. Oxidation-induced embrittlement in polypropylene – a tensile testing study. Polym Degrad Stability 70:333-40, 2000

and this effect is shown in Figure 4 (left).[16] During the induction period, the properties of PP change slowly with time. However, at the induction time, the oxidation reaction becomes autocatalytic, resulting in degradation and an accelerated change in properties. An example of the ability of antioxidants to reduce the time to embrittlement of PP is provided in Figure 4 (right).[17] Two key points may be drawn from these examples. First, the antioxidant should be optimized for the environmental conditions under which the PP device is to be used. Non-optimal concentrations of antioxidants will not provide the maximum extension in service life. Second, even if the antioxidant package is optimized for the specific application, it does not delay oxidation and embrittlement indefinitely. Eventually, embrittlement will occur after all of the antioxidants are depleted. When this occurs, the PP will be unprotected from oxidation.

The key features of oxidation of PP, in terms of the amount of molecular weight loss that is critical for embrittlement to occur, are summarized in Figure 5.[18] An important finding

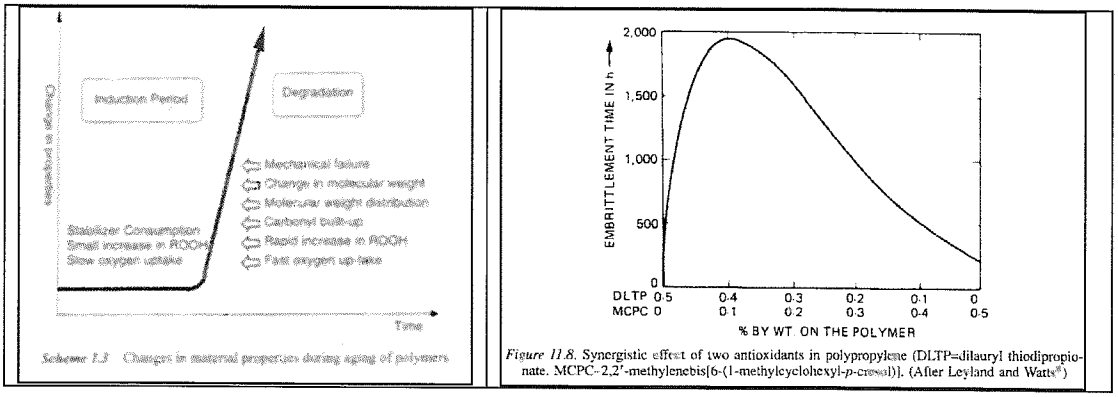

Figure 4. Left: Effect of antioxidant stabilizer on oxidation of polymers. Right: Time to embrittlement for PP stabilized with phenol or DLTDP antioxidants.

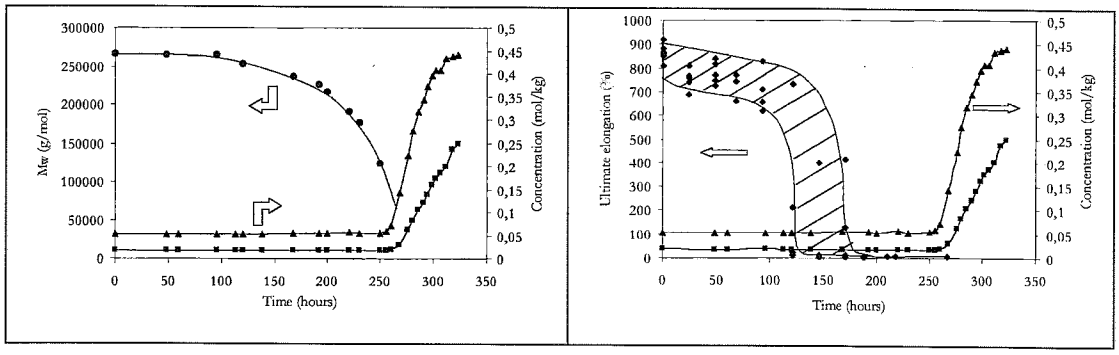

Figure 5. Degradation of unstabilized PP. Left: Change of average molar mass weight Mw (•) during exposure and kinetic curves of carbonyl at 1710 cm^{-1} (■) and of OH groups at 3410 cm^{-1} (triangles) build-up. Right: Evolution of ultimate elongation (◆) during exposure and kinetic curves of carbonyl at 1710 cm^{-1} (squares) and of OH groups at 3410 cm^{-1} (triangles) build-up.

from this study is that embrittlement occurs much earlier (~150 hours) than the induction time (~250 hours) determined by the concentration of hydroxyl groups associated with the

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[16] Plastics Additives Handbook, 6th Edition, 2009, p. 1.
[17] Plastic Materials, John Brydson, 1999, p.261.
[18] Fayolle et al. Oxidation-induced embrittlement in polypropylene – a tensile testing study. Polym Degrad Stability 70:333-40, 2000

hydroperoxide (COOH) under these conditions. Thus, the induction time overestimates the useful life of PP with respect to it mechanical properties.

2) PP Oxidizes ***In Vivo*** After Implantation in the Body

As early as 1976, Liebert et al. reported the oxidation of PP filaments *in vivo* using a subcutaneous implantation model in hamsters. This study determined an induction time of 108 days based on FTIR measurements of hydroxyl (which includes the hydroperoxide COOH) and carbonyl groups (Figure 1). However, Liebert estimated that the induction time for autoxidation under assumed *in vivo* conditions (e.g., 37°C in 3.3% O_2) would be approximately 20 years, which is dramatically longer than the observed value of 108 days. It is now known that this shorter *in vivo* induction time can be explained by the foreign body reaction to implanted biomaterials.[19]

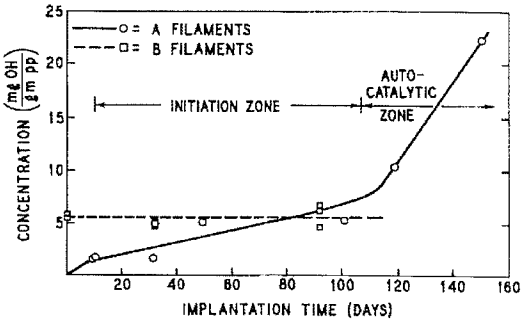

Figure 6. Plot of hydroxyl concentration [OH] vs. implantation time for A (unstabilized) and B (stabilized) PP filaments. From Liebert et al. 1976.

Upon implantation, the body recognizes PP mesh as a foreign body, which elicits an inflammatory response known as the foreign body reaction.[20] In the early stages, monocytes/macrophages migrate to the biomaterial surface, where they can adhere and participate in the events of the foreign body reaction (Figure 7). Adherent macrophages on the surface of the implanted biomaterial fuse to form foreign body giant cells (FGBCs). Adhesion of macrophages and FBGCs at the biomaterial surface results in an isolated microenvironment between the surface of the biomaterial and the plasma membrane of the cell.[21] In a process known as frustrated phagocytosis, macrophages and FBGCs secrete reactive oxygen species (ROS), acids, and enzymes into this microenvironment. Consequently, the surface of the biomaterial is exposed to high concentrations of ROS, and the chemical

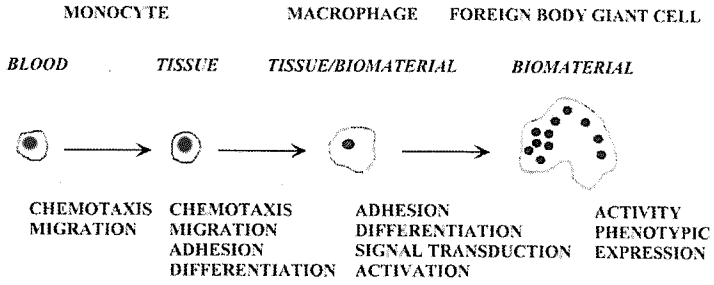

Figure 7. *In vivo* transition from blood-borne monocyte to biomaterial adherent monocyte/macrophage to foreign body giant cell at the tissue/biomaterial interface. There is ongoing research to elucidate the biological mechanisms that are considered to play important roles in the transition to foreign body giant cell development. From Anderson et al. Seminars in Immunology 2008.

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[19] Foreign Body Reaction to Biomaterials. James M. Anderson1,2,*, Analiz Rodriguez1,*, and David T. Chang2. Semin Immunol. 2008 April ; 20(2): 86–100; Zhao et al. Cellular interactions with biomaterials: in vivo cracking of pre-stressed Pellethane 2363-80A. JBMR 24: 621-37, 19990; Zhao et al. Human plasma α2-macroglobulin promotes in vitro oxidative stress cracking of pellethane 2362-80A: in vitro and in vivo correlations. JBMR 27:379-89, 1993

[20] Id.

[21] Id.

composition of the biomaterial will determine its susceptibility to oxidative degradation. As an example, the polyether soft segment of poly(ether urethane)s is known to undergo oxidative degradation. The morphological progression of the foreign body reaction on a poly(ether urethane) surface is shown in Figure 8.[9]

While the initial studies identifying adherent macrophages and FBGCs as sources of ROS focused on poly(ether urethane)s, these cell populations have also been reported to infiltrate PP mesh. In a recent study characterizing the foreign body reaction of PP implants in a rat abdominal wall model, macrophages and foreign body giant cells were observed both in the tissue surrounding the implant and also the implant itself.[22] Thus, within one week after implantation PP mesh is colonized by macrophages and FBGCs. Furthermore, PP mesh samples showed more inflammatory cells than PP sutures.

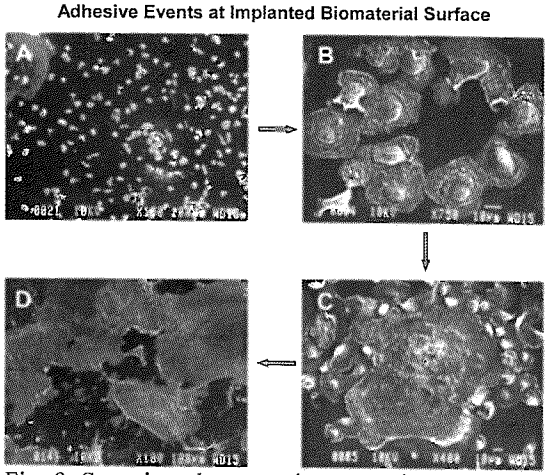

Fig. 8. Scanning electron microscopy images of an Elasthane 80A Polyurethane surface from an in vivo cage study showing the morphological progression of the foreign body reaction. The sequence of events at the Polyurethane surface includes (A) monocyte adhesion (0 days), (B) monocyte-to-macrophage development (3 days), (C) ongoing macrophage-macrophage fusion (7 days), and (D) foreign body giant cells (14 days). From JM Anderson et al., Foreign body reaction to biomaterials. Seminars in Immunology 20:86-100, 2008.

3) The Reactivity and Density of PP Mesh Affect Clinical Outcomes

The development of the Pinnacle and Uphold devices with Polyform mesh, and also those products developed using the Advantage mesh, did not consider the peer-reviewed literature concerning the reactivity of polypropylene and the effects of mesh density on the foreign body reaction. Because the foreign body response will attack the total surface area of the implant, more PP mesh results in an elevated foreign body reaction.[2324] The Pinnacle and Uphold meshes have a relatively large surface area compared to other meshes on the market.[25]

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[22] Tensile strength and host reponse towards different PP implant materials used for augmentation of fascial repair in a rat model. Deprest et al. Int Urogynecol J 18:619-26, 2007.

[23] Anderson Seminars Immunology 2008; J. Otto, E. Kaldenhoff, R. Kirschner-Hermanns, T. Muhl, U. Klinge. Elongation of textile pelvic floor implants under load is related to complete loss of effective porosity, thereby favoring incorporation in scar plates. J Biomed Mater Res A. 2014 Apr;102(4):1079-84. doi: 10.1002/jbm.a.34767. Epub 2013 Jun 11.; W.S. Cobb, K.W. Kercher, and B.T. Heniford.The Argument for Lightweight Polypropylene Mesh in Hernia Repair Surg Innov. Mar;12(1):63-9 (2005); William S. Cobb et al. Textile Analysis of Heavy Weight, M.id-Weight, and Light Weight Polypropylene Mesh in a Porcine Ventral Hernia Model, Journal of Surgical Research; 136, 1-7; 2006; William S. Cobb et al., Normal lntrabdominal Pressure in Healthy Adults, Journal of Surgical Research, Vol. 129, No. 2, December 2005; U. Klinge, el al., Modified Mesh for Hernia Repair that is Adapted to the Physiology of the Abdominal Wall, European Journal of Surgery, Vol. 164; 1998;

[24] *Id*; see also BSCM06100029429; BSCM05200007797; BSCM05200006186

[25] BSCM06100238708; BSCM06100041763; BSCM04800000681

More than a decade after the first research was published on the topic, Dr. Dennis Miller, one of BSC's paid consultants, explained the importance of mesh density in a 2011 presentation entitled "Mesh Engineering, Where are we going? Where have we been?" In it he states:

> …
> "The best graft is no graft
> Goal: Increase anatomic durability
> Avoid: Erosion, Infection, Pain
> Needs: Minimize stiffening/contraction/folding
> Balanced pt response
> -pt immune factors
> -Enhance incorporation
> Reduced Contamination
> Reduced Degradation
> …
> NEW MEASURES
> Surface Area/cm2
> - Fiber diameter
> - Mil thickness
> - Pore size
> Size of implant
> Degradation (toxic compounds released)
> Roughness (wicking)
> Accommodating for contraction
> -Another future role for ultrasound
> -Surgeon can avoid stress response by loose application"[26]

For the decades the literature has stressed the need for less material to reduce adverse events in PP mesh implantees.[27] It has also stressed the effects of the reactivity of PP *in vivo*: "[a]lthough considered nonbiodegradable, the loss of compliance of polypropylene mesh is attributed to its oxidative degradation triggered by the presence of a chronic inflammatory response that can be maintained for years following implantation."[28]

4) The Literature has Confirmed that the Properties of PP Mesh Change After Implantation, Causing Adverse Events.

Most recently, Wood et al. published a comparison of three different explanted synthetic meshes (polypropylene, expanded polytetrafluoroethylene (ePTFE), and polyethylene terephthalate (PET)) from a single patient who had undergone three recurrent ventral hernia

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[26] BSCMO6100068344

[27] Cobb WS, Kercher KW, Heniford BT. The argument for light-weight polypropylene mesh in hernia repair. Surg Innov 2005;12:63–69; Klinge U, Klosterhalfen B, Muller M, Schumpelick V. Foreign body reaction to meshes used for the repair of abdominal wall hernias.
Eur J Surg 1999;165:665–673.

[28] Alexander Huber, Alan V. Boruch, Alejandro Nieponice, Hongbin Jiang,Christopher Medberry, Stephen F. Badylak. Histopathologic host response to polypropylene-based surgical mesh materials in a rat abdominal wall defect model.

repairs.[29] Implantation times for the meshes were 3 years for the PP and PET meshes and 2 years for the ePTFE mesh. SEM images of explanted PP "showed significant surface cracking" while the PET and ePTFE meshes did not. FTIR analysis also confirmed PP degradation from "free radical formation and oxidation of the polypropylene mesh while *in vivo."*

The Wood study supports the conclusions published by Clavé et al., which examined explanted pelvic meshes for degradation. Clavé reported that 42% of the explants showed evidence of chronic inflammation, characterized by an infiltrate of mononuclear cells and FGBCs. SEM analysis revealed that the implants were degraded, and that degradation was readily observed in meshes that had been implanted for at least 3 months.[30]

The findings of the Clavé study findings reinforced work done by Costello et al., who reported PP mesh oxidation and embrittlement as being a cause of mesh degradation and complications *in vivo*.[31] Costello derived his conclusions from comparisons made between pristine and explanted samples via molecular weight, SEM imaging, and compliance testing. Those authors reported that all three of these methods confirmed that PP mesh had degraded *in vivo*, most likely by oxidation.[32]

In another study evaluating non-degradable meshes explanted from 17 patients that had surgery for repair of abdominal wall defects, a foreign body reaction characterized by granulation tissue and inflammatory cells 3 – 24 months post-implantation was seen.[33] The PP meshes from this study showed more inflammatory cells and fibroblasts near the mesh interface when compared to PTFE and polyester. And yet another study investigated 14 explanted mesh samples observed by SEM that 85% of the samples showed evidence of cracking, fissures, and peeling.[34] After host tissue was removed, the mesh samples remained folded and contracted, evidencing that mesh samples were permanently changed after implantation.

5) **Mechanical and other *in vivo* Stresses, including those from the Foreign Body Reaction, cause the Properties of Implanted BSC PP Mesh to Deteriorate.**

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[29] Wood, A.J., et al. *Materials Characterization and Histological Analysis of Explanted Polypropylene, PTFE, and PET hernia meshes from an Individual Patient*. J. MATER. SCI. MATER. MED. 24(4): 1113-1122 (2013).

[30] Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J (2010) 21:261-270

[31] Characterization of heavyweight and lightweight polypropylene prosthetic mesh explants from a single patient. Surg Innov. 14:168–176 Costello CR, Bachman SL, Grant SA, Cleveland DS, Loy TS, Ramshaw BJ (2007); Materials characterization of explanted polypropylene hernia meshes. J Biomed Mater Costello CR, Bachman SL, Grant SA (2007) Res Part B: Appl Biomater 83B:44-49

[32] *Id.*

[33] Foreign Body Reaction to Meshes Used for the Repair of Abdominal Wall Hernias. U. Klinge,1,3 B. Klosterhalfen,2,3 M. Mu¨ller1 and V. Schumpelick1. Eur J Surg 1999; 165: 665–673

[34] Explants from a single patient. Surg Innov 14(3):168-176 80. Costello CR, Bachman SL, Grant SA (2007) Materials characterization of explanted polypropylene hernia meshes. J Biomed Mater. Res Part B: Appl Biomater 83B:44-49

All implantable medical devices are susceptible to the dynamic nature of the environment in which they are implanted. Environmental stress cracking of implanted biomaterials is controlled by three factors: (1) residual stress in the biomaterial, (2) a source of chemical degradation in the body, and (3) the chemical structure of the biomaterial.[35] Poly(ether urethane)s used as pacemaker lead insulation are an example of how oxidation of an implanted biomaterial can lead to Environmental Stress Cracking (ESC) and device failure. While poly(ether urethane) elastomers were believed to be biocompatible for many years, they are now known to undergo ESC due to oxidative degradation of the polyether component and subsequent loss in molecular weight.[36] As shown in Figure 9, adherent macrophages and FBCGs were responsible for environmental stress cracking of poly(ether urethane)s *in vivo*.[37] A later study found that *in vivo* stress cracking of this poly(ether urethane) was reproduced *in vitro* by treating pre-stressed polymer specimens with an oxidative medium (10% hydrogen peroxide with 0.10 M cobalt chloride).[38] Under these conditions simulating the isolated microenvironment between the surface of the biomaterial and the cell, *in vitro* stress cracking was similar in appearance to that observed *in vivo*. Furthermore, infrared spectroscopy showed that ROS participated in the oxidative degradation process.[39]. Thus, oxidative degradation and environmental stress cracking have a synergistic effect on the failure of poly(ether urethane) catheter lead insulation, by which oxidative degradation drives the embrittlement of the polymer surface and its subsequent cracking, which in turn exposes new surfaces of the material to oxidative degradation and ultimately clinical device failure.[40]

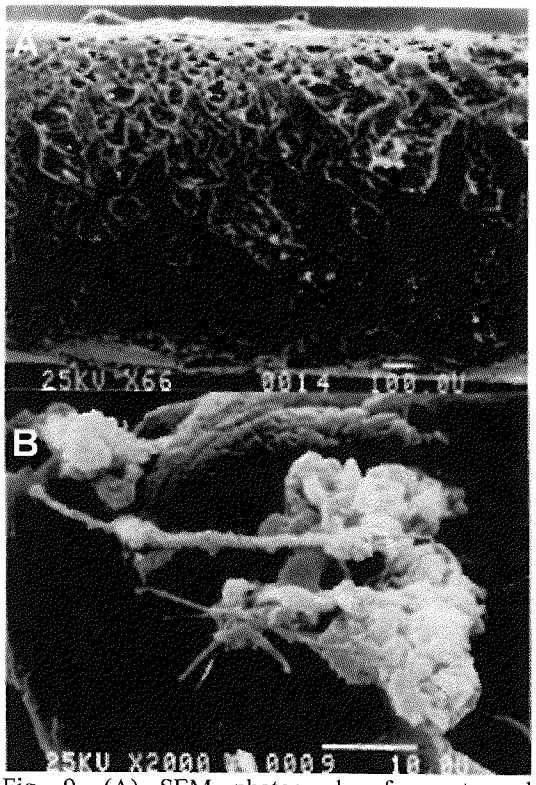

Fig. 9. (A) SEM photograph of pre-stressed Pellethane 80A specimen implanted for 5 weeks. The specimen had severe cracking. Original magnification x66. (B) SEM photograph (at higher magnification) of pre-stressed Pellethane 80A specimen implanted for 5 weeks. Cellular adhesion was present. Original magnification x2000. From Zhao et al. JBMR 24:621, 1990.

Similar to poly(ether urethane)s, PP is also susceptible to oxidative degradation, which

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[35] Anderson et al. Cellular interactions with biomaterials: in vivo cracking of pre-stressed Pellethane 2363-80A. JBMR 24: 621-37, 1990.
[36] *Id.*
[37] Zhao et al. JBMR 24:621, 1990.
[38] Zhao et al. JBMR 27:379-89, 1993.
[39] Wiggins MJ, Wilkoff B, Anderson JM, Hiltner A. Biodegradation of polyether polyurethane inner insulation in bipolar pacemaker leads. J Biomed Mater Res 2001;58(3):302–7
[40] James M. Anderson1,2,*, Analiz Rodriguez1,*, and David T. Chang2. Foreign Body Reaction to Biomaterials. Semin Immunol. 2008 April ; 20(2): 86–100.

results in chain scission and loss of ductility (e.g., embrittlement).[41] Embrittlement occurs at a very low conversion in the chain scission process, and surface embrittlement of the PP fibers leads to crack initiation. Mechanical stress on the fibers will in turn enhance stress cracking and expose new PP surface to the oxidative environment. The amount and type of mechanical stress that is placed in the Advantage and Polyform meshes *in vivo*, however, has not been studied by BSC.[42] In a study presented at the 38th Annual IUGA meeting in Dublin, Ireland, researchers used a sheep model to explain differences in clinical outcomes between PP meshes implanted abdominally to those implanted vaginally.[43] The mechanical forces in the vaginal wall were found to differ substantially from those in the abdominal wall. The results showed an 8.4-fold higher contraction rate in the vaginally implanted meshes when compared to their abdominal counterparts. Furthermore, vaginal implantation of PP mesh led to higher rates of exposure and folding when compared to abdominal implantation. This sheep study indicates that PP mesh implanted vaginally is subject to greater mechanical stresses than mesh implanted abdominally. Higher mechanical stress directly correlates with increased environmental stress cracking, which can lead to adverse events. Boston Scientific could have performed a similar sheep study at any time point prior to or after the launch of the products containing its Advantage and Polyform meshes to evaluate their performance in their intended environment, but has not.

6) BSC has not Investigated the Effects of PP Oxidation after Implantation

Despite the considerable evidence present in the scientific literature regarding the foreign body response and the susceptibility of PP to degradation, there is no evidence that BSC has investigated the potential for harm that degradation of PP can have on those who are implanted with products containing Advantage or Polyform meshes. Moreover, throughout all of these products' lifecycles, principle scientists at BSC have repeatedly ignored the available research and concluded that PP is inert.[44] When confronted with the question, BSC performed only a historical analysis of PP *in vivo* and concluded that PP is inert after implantation.[45] Furthermore, BSC was made aware that the resin used to make its PP meshes was not inert via Material Safety Data Sheet (MSDS) that accompanied BSC's Marlex polypropylene; it states:

> ...
> Section 10 (Stability and reactivity): Incompatibility With Other Materials: May react with oxygen and strong oxidizing agents, such as chlorates, nitrates, peroxides, etc.[46]
> ...

If it were true that PP was inert, then it would not react with anything. Although PP can never be considered inert, it is often stabilized against oxidation by adding antioxidants to

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[41] Fayolle et al. Initial steps and embrittlement in the thermal oxidation of stabilized polypropylene films. Polym Degrad Stability 75:123-9, 2002
[42] BSCM01400000001-347; BSCM00100000001-210; BSCM02900000001-456; BSCM01300000001-585; BSCM01200000001-92; BSCM03200006203
[43] Comparison of contraction and exposure rate following vaginal as opposed to abdominal implantation of flat mesh/polypropylene implant. I. Urbankova, A. Feola, S. Manodoro, J.Vlacil, M. Endo, D. De Ridder, J. Deprest. Urogynecol J (2013) 24 (Suppl 1):S1–S152
[44] BSCM07400018360
[45] BSCM05100122946
[46] BSCM01300000542

the molten polymer.[47] Stabilization can be tailored to fit specific applications, but in the case of the resin used to make the Advantage and Polyform meshes, known as Marlex HGX-030-01, the antioxidants present are only intended to protect it during processing and long-term storage and not against other *in vivo* stresses such as ROS or mechanical forces.[48]

The antioxidants in Marlex HGX-030-01 resin are known as Irganox 3114 and Irgafos 168.[49] Irganox 3114 is a sterically hindered phenolic antioxidant that is intended to protect the polymer during both thermal processing and long-term storage. Irgafos 168 is an organo-phosphite antioxidant that is expected to be expended during processing. Neither of these antioxidants can be expected to protect against reactive oxygen species in the *in vivo* environment where the mesh is placed.[50]

While the presence of antioxidants in the Advantage and Polyform meshes will likely extend the time to embrittlement, how long it will be extended has not been studied. It is important to note that embrittlement occurs at early time points and prior to the onset of autocatalytic degradation. Thus, this cycle of antioxidant depletion followed by PP oxidation and eventual embrittlement of the surface of the mesh will not stop until all of the mesh is removed, since cracking exposes new surfaces to ROS and the reaction begins on newly exposed mesh surface.

The resin used to make the Advantage and Polyform meshes, Marlex® HGX-030-01, was manufactured by Phillips Sumika (now Conoco Phillips).[51] The chemical reactivity of this resin and the potential for its degradation is well described by its manufacturer:

> "Marlex® polypropylene has good chemical resistance to most mineral acids and bases, but like other polyolefins, can be attacked by some strong mineral acids, halogens, and oxygen. The effect of strong oxidizing agents is an attack on the polymer chain resulting in eventual embrittlement of the resin."[52]

Furthermore, Phillips Sumika made it clear the resin was not to be used as BSC is using it in its mesh products. The Material Safety Data Sheet for Marlex® HGX-030-01 states:

> "MEDICAL APPLICATION CAUTION: Do not use this Phillips Sumika Polypropylene Company material in medical applications involving permanent implantation in the human body or permanent contact with internal body fluids or tissues."[53]
>
> ...
>
> "Incompatibility With Other Materials: May react with oxygen and strong oxidizing agents, such as chlorates, nitrates, peroxides, etc."[54]

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[47] E. Rene de la Rie. Polymer Stabilizers. A Survey with Reference to Possible Applications in the Conservation Field. Studies in Conservation 33(1988) 9-22
[48] CP-00183
[49] CP-00081
[50] CP-00183
[51] CP-00183
[52] CP-00092
[53] BSCM 11600009696; BSCM05100117275
[54] *Id.*

This information was known by BSC, but there is no evidence I have seen that this information was heeded.

7) The Presence of Antioxidants does not Guard Against Degradation of BSC Meshes after Implantation.

The enduring nature of the foreign body reaction emphasizes the need for antioxidants to be added to biomaterials such that the time to embrittlement is elongated.[55] PP in its pure (i.e., unstabilized) form degrades rapidly *in vivo*, with an induction period of only 108 days[56], and carbonyl groups were detected in unstabilized PP by infrared spectroscopy within 50 – 90 days.[57] Liebert et al. also tested stabilized PP in the hamster subcutaneous implant model. Oxidation of stabilized PP was observed, but the experiment ended at 100 days, at which time induction had not been observed for stabilized PP filaments. Consequently, the *in vivo* induction time for stabilized PP has not been reported.

As shown in Figure 4, antioxidants will not stabilize PP indefinitely. Furthermore, the antioxidant package must be optimized for the intended use to achieve maximum usable life of the polymer. However, neither of the antioxidants in the Marlex HGX-030-01 resin used to manufacture Advantage and Polyform meshes is intended to protect against the ROS secreted by inflammatory cells *in vivo*.[58] While the presence of antioxidants in the BSC meshes will likely extend the time to embrittlement, how long it will be extended has also not been studied by Boston Scientific even though there are tests that can be done. Moreover, because in vivo oxidation and embrittlement is an ongoing process, the PP mesh is unstable and its properties change with time.

The induction time for stabilized PP can be estimated from a simple *in vitro* oxidative degradation test that was first published in 1993 by the J.M. Anderson group: Zhao et al. "Human plasma α_2-macroglobulin promotes in vitro oxidative stress cracking of Pellethane 2363-80A: In vivo and in vitro correlations." *Journal of Biomedical Materials Research* 27:379-89, 1993. As of October 26, 2014, this paper has been cited 82 times according to Google Scholar.

In collaboration with Dr. Dunn (Polymer and Chemical Technologies), I have investigated the oxidative degradation of the Advantage and Lynx meshes by this *in vitro* testing method. The objective of the test was to determine whether the induction time of mesh samples taken from exemplar Advantage and Lynx SUI products, as well as that from an exemplar Ethicon TVT, was higher than that of unstabilized PP. The experiment used a protocol from a more recent study published by the Anderson group in 1997 (cited 76 times). In this protocol, specimens were incubated at 37°C (physiological temperature) in an aqueous solution containing 20% H_2O_2 and 0.1 M cobalt chloride. The cobalt chloride catalyzes the decomposition of the hydrogen peroxide to form hydroxyl radicals that attack the PP. This solution replicates the microenvironment in the pocket between the adherent macrophage and the surface of the biomaterial.[59] Furthermore, this *in vitro* oxidative

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[55] James M. Anderson1,2,*, Analiz Rodriguez1,*, and David T. Chang2. Foreign Body Reaction to Biomaterials. Semin Immunol. 2008 April ; 20(2): 86–100.
[56] Liebert et al. Subcutaneous implants of PP filaments. JBMR 10:939-51, 1976.
[57] Id.
[58] CP-00183
[59] Zhao et al. JBMR 1993

system was reported to duplicate ESC of poly(ether urethane)s *in vivo*.[60] I have published two papers in the scientific journal *Biomaterials*, one in 2011 (cited 33 times) and one in 2014 (cited 3 times), using the same 20% H_2O_2 /0.1 M cobalt chloride system to measure the oxidative degradation rate of poly(ester urethane) and poly(thioketal urethane) scaffolds. Thus, this *in vitro* oxidative degradation test is well established in the scientific literature, and was available to Boston Scientific at the time it developed all of the meshes at issue in this report. In the experiment with Dr. Dunn, unstabilized PP pellets (control), Ethicon TVT, BSC Advantage mesh, and BSC Lynx mesh were incubated in the oxidative solution at 37°C for up to 5 weeks. Dr. Dunn performed the experiment in his chemistry laboratory at Vanderbilt University in consultation with me.

The results from the *in vitro* degradation testing are presented in Appendix G (Advantage), Appendix H (Lynx), and Appendix I (unstabilized PP) of Dr. Dunn's expert report. I have reviewed these data and drawn several conclusions. First, the FTIR spectra for unstabilized PP pellets reveal substantial increases in the hydroxyl and carbonyl peaks at week 4. Similarly, the XPS data show a substantial increase in the R-C-OOH peak from week 3 to week 4. These data indicate an induction time of ~4 weeks (28 days) for unstabilized PP under *in vitro* oxidation conditions, compared to 108 days *in vivo* found by Liebert et al. Thus, the *in vitro* test appears to accelerate degradation by a factor of approximately 4. For TVT, Advantage and Lynx meshes used in this experiment, the increase in hydroxyl and carbonyl peak area occurs from week 4 to 5, suggesting a less than 5 week (35 day) induction period in this medium. Assuming that degradation occurs 4 times faster under *in vitro* compared to *in vivo* conditions, as reported by Liebert et al, these data predict an *in vivo* induction time of ~135 days for the PP in the TVT, Advantage and Lynx meshes.

The SEM micrographs in Dr. Dunn's appendices for this experiment also reveal degradation of Advantage and Lynx PP meshes, as shown in Figure 10. Mesh not exposed to *in vitro* oxidizing medium did not show evidence of pitting on the surface. However, mesh exposed to the *in vitro* oxidizing medium for 5 weeks showed evidence of pitting on the surface.

These *in vitro* data are consistent with the opinion exemplified in Figure 4 that antioxidants do not

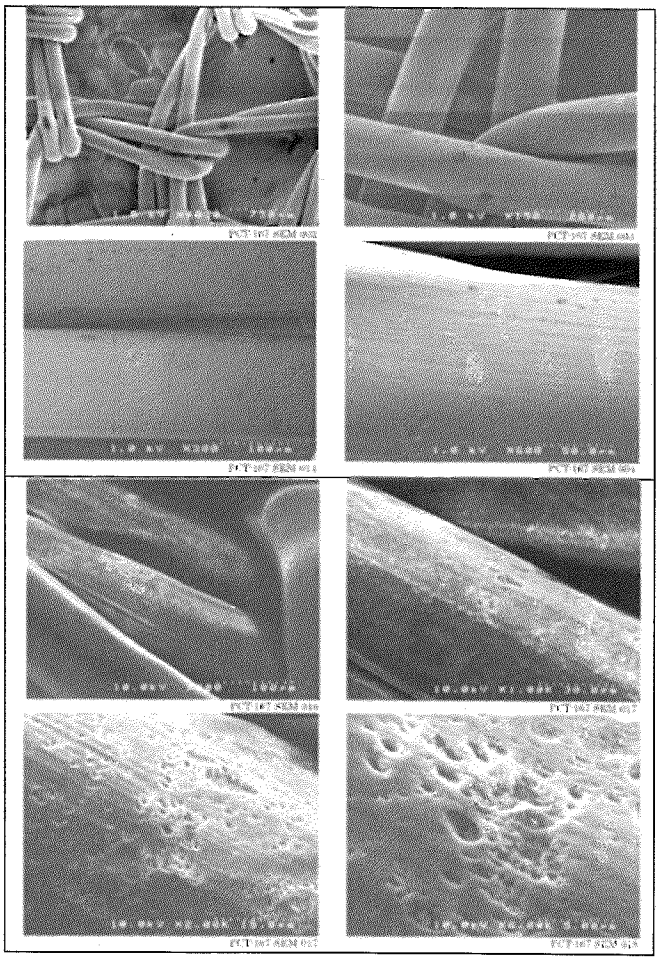

Figure 10. SEM images of Exemplar Advantage Fit Transvaginal Mid-Urethral Sling System. Top 4 panels: Mesh not exposed to *in vitro* oxidizing medium. Bottom 4 panels: Mesh exposed to *in vitro* oxidizing medium for 5

[60] Id.

protect the mesh for an infinite period of time and are eventually depleted. After depletion of the antioxidants, the PP is not protected and will react with ROS, resulting in embrittlement. Importantly, the *in vitro* oxidation test method described herein was available to Boston Scientific at the time that the Advantage and Polyform meshes were developed and could have been used to optimize the antioxidant package and determine the induction time of the PP mesh. However, I have seen no evidence that Boston Scientific performed *in vitro* oxidation testing of its pelvic meshes.

The three requirements for environmental stress cracking are (1) stress on the biomaterial, (2) a source of reactive oxygen, and (3) a biomaterial with a chemical structure rendering it susceptible to oxidation.[61] Applying what is known regarding the intended environment where these meshes are placed, it is apparent that: (1) the forces exerted on the mesh after implantation will vary greatly from patient to patient; (2) the scientific literature has confirmed that adherent macrophages and FBGCs are present on the PP mesh *in vitro*, and that these cells secrete ROS which reacts with the mesh; and (3) the scientific literature and our *in vitro* testing separately confirm that PP degrades by oxidation. Thus, all three requirements are present when PP mesh is implanted in the pelvic floor. This cycle of depletion of antioxidants through reaction with ROS followed by the eventual embrittlement of the surface of the mesh surface will not stop until all of the mesh is removed, since cracking exposes new surfaces to ROS and the reaction begins anew.[62]

8) Plaintiff Specific Opinions

As part of my training and research in biomaterials, I routinely review histopathology including tissue samples and slides containing explanted material and devices. I have the relevant expertise and have published papers with detailed histologic and histomorphometric analyses of scaffolds designed for healing of soft tissue and bone.[63]

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[61] Anderson et al. Cellular interactions with biomaterials: in vivo cracking of pre-stressed Pellethane 2363-80A. JBMR 24: 621-37, 1990.
[62] Anderson Seminar Immunol 2008

[63] *EM Prieto*, *AD Talley*, S, Drapeau, K Kalpakci, SA Guelcher*. Effects of particle size and demineralized bone matrix on remodeling of settable bone grafts in a rabbit femoral condyle defect model. *Journal of Biomedical Materials Research Part B: Applied Biomaterials* In Review; *EJ Adolph*, JM Davidson, SA Guelcher, LB Nanney*. Biodegradable polyurethane scaffolds promote healing in a porcine full-thickness excisional wound model. *Journal of Biomaterials Science: Polymer Edition* DOI:10.1080/09205063.2014.965997 Oct 7, 2014; *AJ Harmata*, CL Ward, *KJ Zienkiewicz*, JC Wenke, SA Guelcher*&. Investigating the Effects of Surface-Initiated Polymerization of ε-Caprolactone to Bioactive Glass Particles on the Mechanical Properties of Settable Polymer/Ceramic Composites. *Journal of Materials Research* 29: 20, 2014; JL Martin, MK Gupta, *JM Page*, F Yu, JM Davidson, SA Guelcher, CL Duvall*. Synthesis of a Porous, Biocompatible Tissue Engineering Scaffold Selectively Degraded by Cell-Generated Reactive Oxygen Species. *Biomaterials* 35(12):3766-76, 2014.; *JE Dumas*, *EM Prieto*, *KJ Zienkiewicz*, T Guda, JC Wenke, JM Bible, GE Holt, SA Guelcher*. Remodeling of Settable Allograft Bone/Polymer Composites with Initial Bone-like Mechanical Properties in Rabbit Femora. *Tissue Engineering Part A* 20(1-2):115-29, 2014; *JM Page*, *EM Prieto*, *JE Dumas*, *KJ Zienkiewicz*, JC Wenke, P Brown-Baer, SA Guelcher*. Reactivity and biocompatibility of injectable polyurethane/allograft bone biocomposites. *Acta Biomaterialia, 8:4405–4416, 2012; JE Dumas*, P Brown-Baer, *EM Prieto*, T Guda, R Hale, JC Wenke, SA Guelcher*&. Injectable reactive biocomposites for bone healing in critical-size rabbit calvarial defects. *Biomedical Materials* 7(2): 024112, 2012; *EJ Adolph, AE Hafeman*, KL Zienkiewicz, JM Davidson, SA Guelcher*. Injectable biodegradable polyurethane scaffolds for wound healing. *Journal of Biomedical Materials*

I have reviewed images of histological sections of explants taken from from Ms. Hembree, Ms. Nava, Ms. Parker, Ms. Robinson, Sharon Beehler, Ms. Hanson, and Lori Hoffman. One group of slides was stained with hematoxylin and eosin (H&E) stain, while the other was stained with primary antibodies to myeloperoxidase and counter-stained with hematoxylin. I have determined that there are adherent macrophages and/or foreign body giant cells near the surface of the polypropylene mesh in all cases. I have also observed positive staining for myeloperoxidase in all 7 patient explants. Staining for myeloperoxidase was most intense near the surface of the PP.

In all instances, the presence of macrophages and/or FBGCs, as well as the evidence of myeloperoxidase, is consistent with what the peer-reviewed literature has reported with respect to the effects of secreted ROS on biomedical implants.[64]

Research Part A 100A: 450–461, 2012. PMC328836; Guelcher SA, Brown KV, *Li B*, Guda T, *Lee BH*, and JC Wenke*[&]. Dual-purpose bone grafts improve healing and reduce infection. *Journal of Orthopaedic Trauma* 25(8):477-82, 201; K Brown, *B Li*, T Guda, DS Perrien, SA Guelcher, JC Wenke*. Improving Improving bone formation in a rat femur segmental defect by controlling BMP-2 release. *Tissue Engineering Part A* 17(13-14): 1735-1746, 2011; *AE Hafeman, KJ Zienkiewicz*, AL Zachman, HJ Sung, LB Nanney, JM Davidson, SA Guelcher*. Characterization of degradation mechanisms of biodegradable lysine-derived aliphatic polyurethanes. *Biomaterials* 32(2):419-29, 2011. PMC29973472; *B Li*, JM Davidson, and SA Guelcher*. The effect of the local delivery of platelet-derived growth factor (PDGF-BB) from reactive two-component polyurethane scaffolds on the healing in rat skin excisional wounds. *Biomaterials* 30:3486–3494, 2009.

[64] Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J (2010) 21:261-270; Anderson et al. Cellular interactions with biomaterials: in vivo cracking of pre-stressed Pellethane 2363-80A. JBMR 24: 621-37, 1990; James M. Anderson1,2,*, Analiz Rodriguez1, and David T. Chang2. Foreign Body Reaction to Biomaterials. Semin Immunol. 2008 April ; 20(2): 86–100;

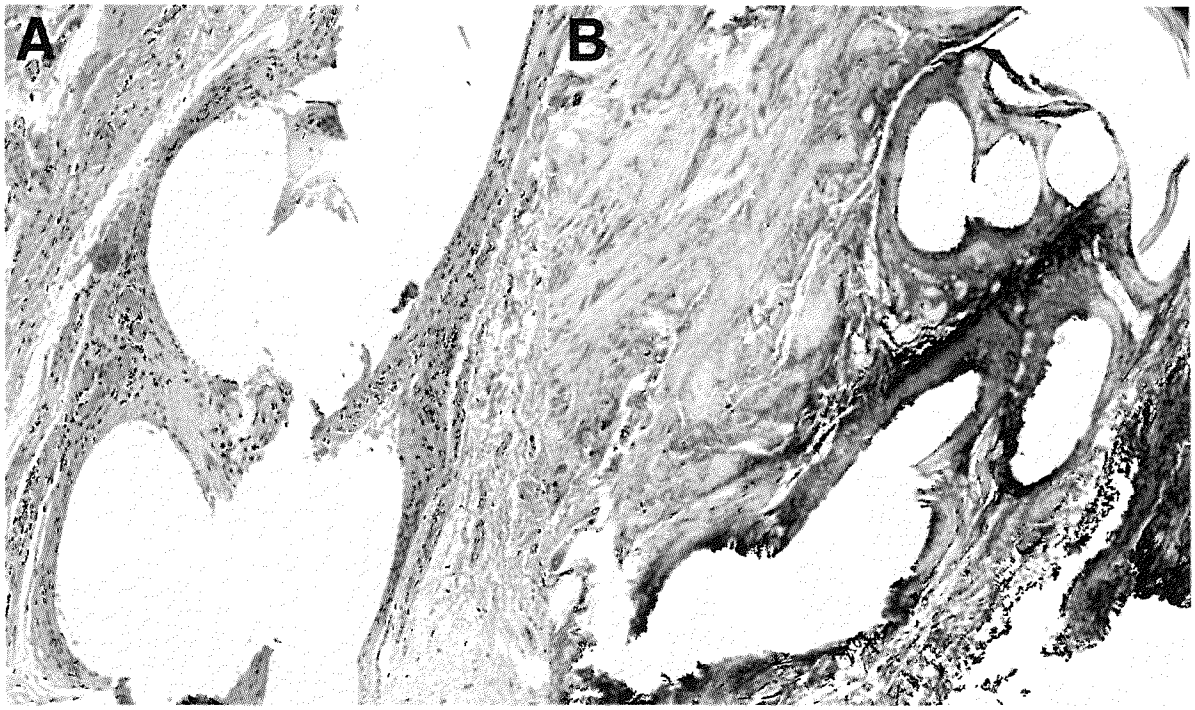

Figure 1. Images of histological sections of PP mesh explanted from Ms. Hembree stained with (A) Hematoxylin & Eosin (H&E) and (B) a primary antibody to myeloperoxidase.

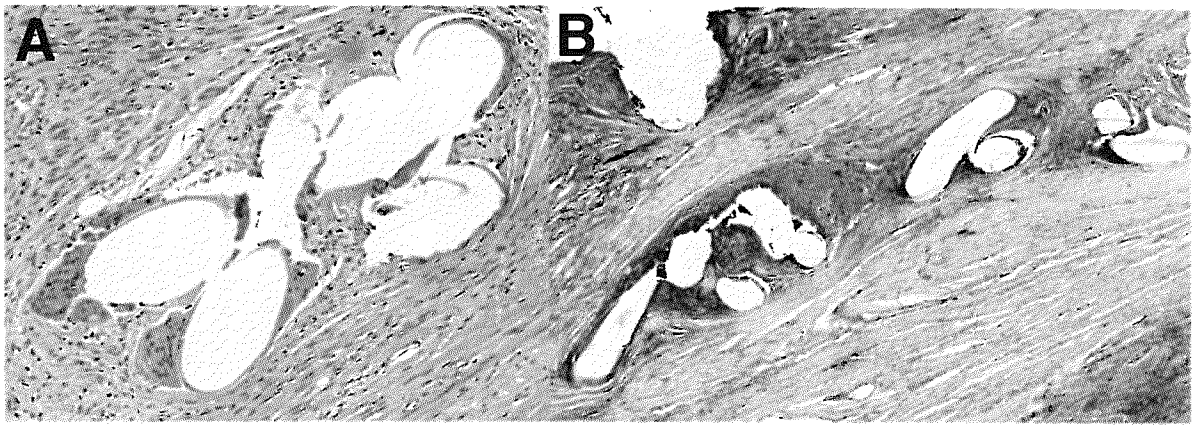

Figure 2. Images of histological sections of PP mesh explanted from Ms. Nava stained with (A) Hematoxylin & Eosin (H&E) and (B) a primary antibody to myeloperoxidase.

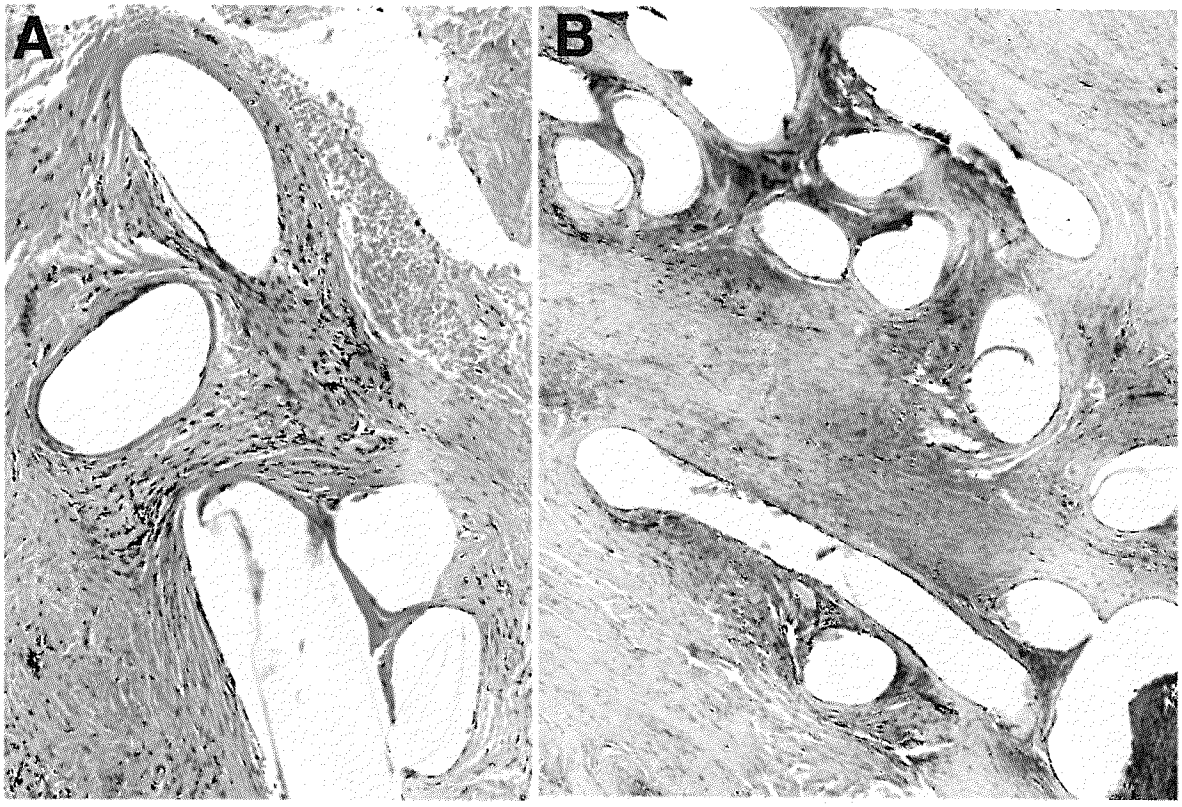

Figure 3. Images of histological sections of PP mesh explanted from Ms. Parker stained with (A) Hematoxylin & Eosin (H&E) and (B) a primary antibody to myeloperoxidase.

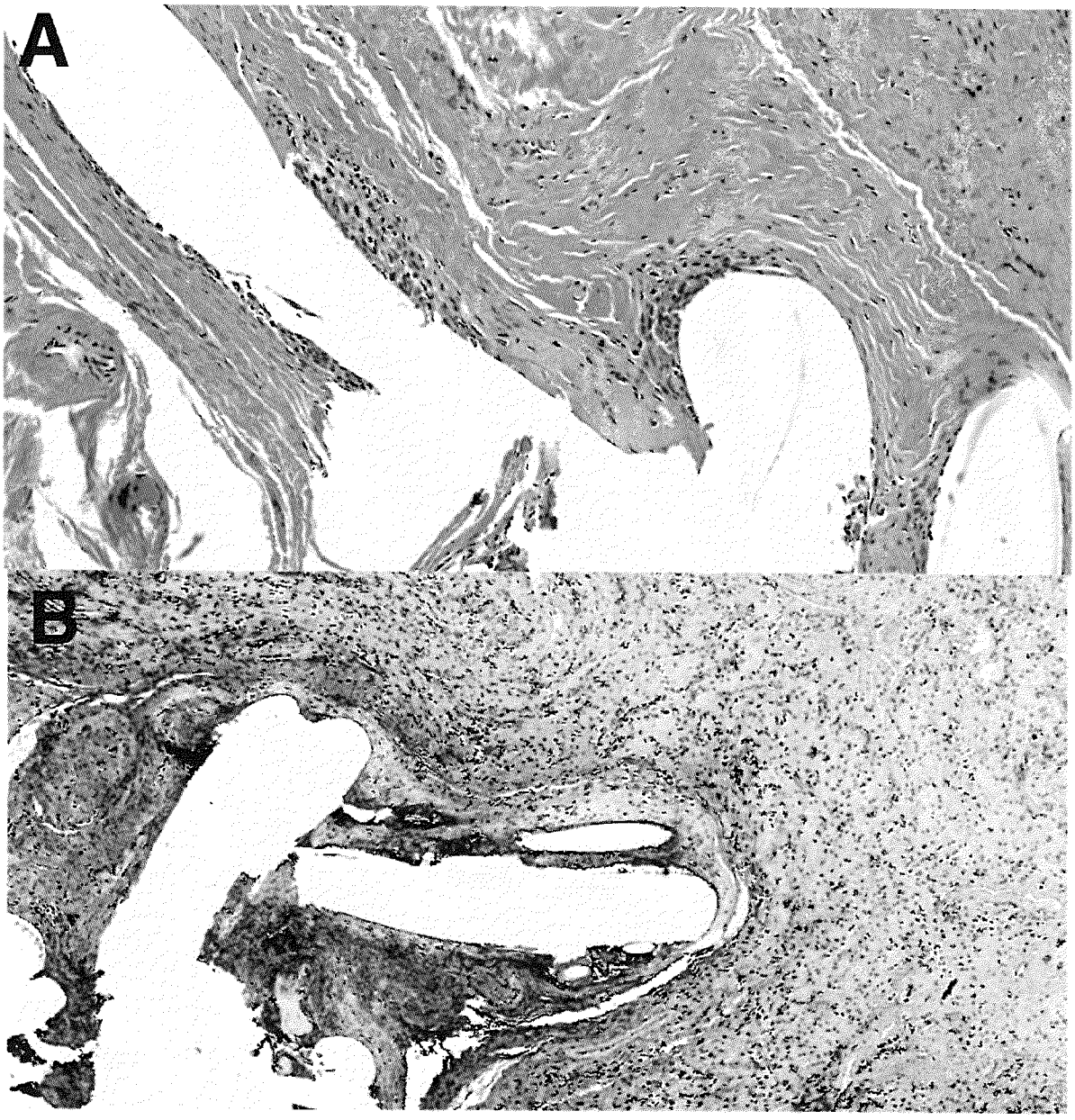

Figure 4. Images of histological sections of PP mesh explanted from Ms. Robinson stained with (A) Hematoxylin & Eosin (H&E) and (B) a primary antibody to myeloperoxidase.

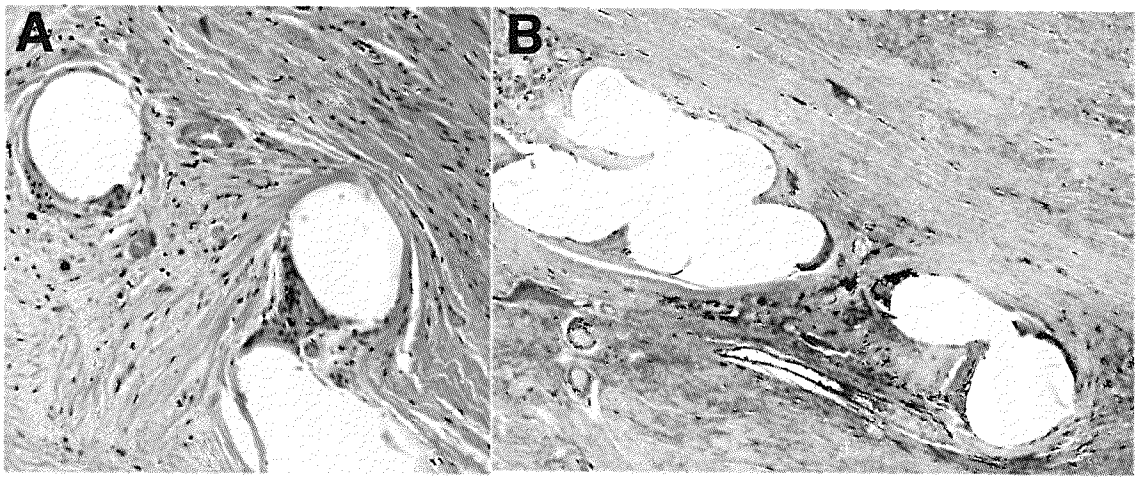

Figure 5. Images of histological sections of PP mesh explanted from Ms. Sharron Beehler stained with (A) Hematoxylin & Eosin (H&E) and (B) a primary antibody to myeloperoxidase.

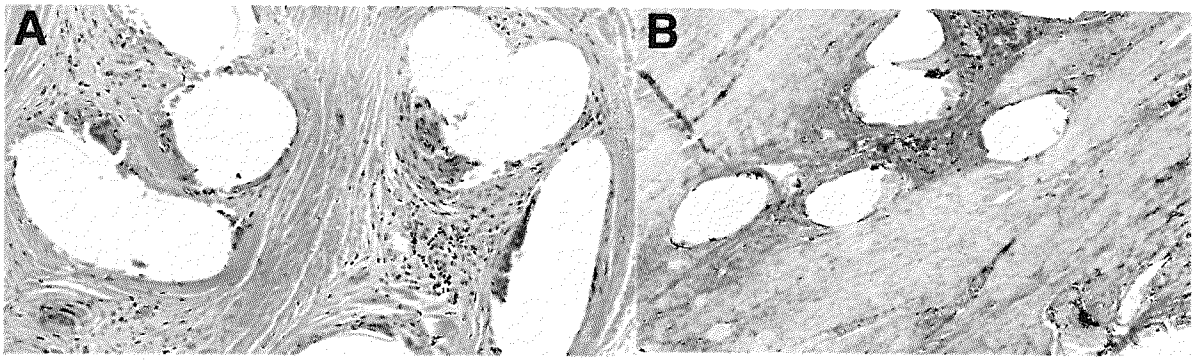

Figure 6. Images of histological sections of PP mesh explanted from Ms. Hanson stained with (A) Hematoxylin & Eosin (H&E) and (B) a primary antibody to myeloperoxidase.

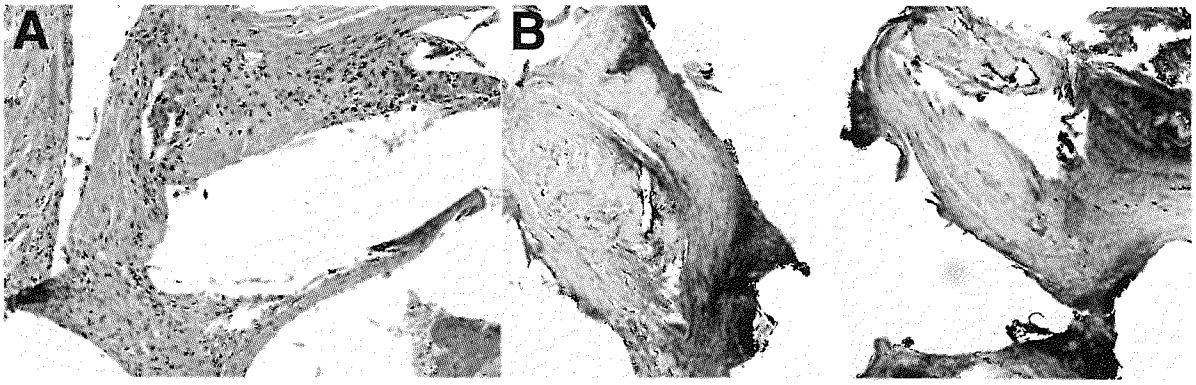

Figure 7. Images of histological sections of PP mesh explanted from Ms. Lori Hoffman stained with (A) Hematoxylin & Eosin (H&E) and (B) a primary antibody to myeloperoxidase.

V. FACTS OR DATA CONSIDERED IN FORMING OPINIONS

The opinions and the bases for those opinions are set forth above. In addition to my knowledge, skill training and experience as an engineer, I have reviewed the following depositions of BSC employees and the exhibits thereto: Rao, Montgomery, Gardner, Goddard, Sherry, Conner, and Intoccia. I have also reviewed the testimony and reports given by defense expert witness, Dr. Badylak, in conjunction with several BSC trials, and the other relevant testimony thereto. I have also considered the material identified in the included listing of reliance documents.

LISTING OF CASES IN WHICH TESTIMONY HAS BEEN GIVEN IN THE LAST FOUR YEARS

IN RE PELVIC MESH AMS LITIGATION SERRANO ET AL—September 2013

IN RE PELVIC MESH BOSTON SCIENTIFIC LITIGATION—February 2014

IN RE PELVIC MESH ETHICON LITIGATION HUSKEY ET AL—April 2014

EXHIBITS WHICH I PLAN TO USE AS A SUMMARY OF OR IN SUPPORT OF OPINIONS

All the Exhibits which I plan to use as summary of or in support of my opinions have not yet been determined, but they include, but are not limited to:

1) Exhibits extracted from the materials I have reviewed;
2) Excerpts from learned treatises and literature;
3) Materials listed above;

Any additional materials to be used will be timely disclosed.

VI. COMPENSATION

The compensation per hour which I expect to be paid for my review, study and testimony is as follows: $285.00 per hour for review and study, $385.00 per hour for deposition and trial testimony time.

Scott A. Guelcher, Ph.D.